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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/058,546	04/10/98	GUNZBURG W	GSF98-02A

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EXAMINER	
WILSON, M	
ART UNIT	PAPER NUMBER
1633	4

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/058,546	Applicant(s) Gunzberg et al.
	Examiner Wilson, Michael C.	Group Art Unit 1633

☐ Responsive to communication(s) filed on _____ .

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-32* is/are pending in the application.

Of the above, claim(s) *5-7, 12, 18, 24, 25, 29, and 30* is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-4, 8-11, 13-17, 19-23, 26-28, 31, and 32* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Election/Restriction

1. Restriction to one of the following inventions is required under 35 U.S.C. 121:

   I. Claims 1-4, 8-11, 13-17, 19-23, 26-28, 31 and 32, drawn to DNA, classified in class 536, subclass 23.1.

   II. Claims 1, 5-7, 8-10, 12-16, 18, 20, 24, 25, 29 and 30, drawn to antisense, classified in class 536, subclass 24.5.

The inventions are distinct, each from the other because of the following reasons: Inventions I and II are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In the instant case the different inventions have different modes of operation because a vector comprising DNA functions to express a protein of interest while a vector encoding antisense functions to produce a polynucleotide that prevents expression of a protein by binding DNA. DNA can be used to replace a protein deficiency while preventing expression using antisense can be used to prevent overexpression. Therefore, DNA and antisense have different functions and different uses. The vectors encoding DNA are not required for the vectors encoding antisense and the vectors encoding antisense are not required for vectors encoding DNA. Considerations for functional levels of protein expression of required for DNA expression vectors are not required for antisense

and consideration for antisense to prevent expression are not required for DNA. Claims 1, 8-10, 13-16 and 20 are generic to groups I and II. These claims will be examined based on the nature of the elected invention.

Because these inventions are distinct for the reasons given above and have acquired a separate status in the art as shown by their different classification, restriction for examination purposes as indicated is proper.

Because these inventions are distinct for the reasons given above and the search required for Group I is not required for Group II, restriction for examination purposes as indicated is proper.

Because these inventions are distinct for the reasons given above and have acquired a separate status in the art because of their recognized divergent subject matter, restriction for examination purposes as indicated is proper.

During a telephone conversation with Anne Collins on 5-3-99 a provisional election was made with traverse to prosecute the invention of DNA, claims 1-4, 8-11, 13-17, 19-23, 26-28, 31 and 32. Affirmation of this election must be made by applicant in replying to this Office action.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a petition under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(I).

Claims 5-7, 12, 18, 24-25, 29 and 30 are withdrawn from consideration as being drawn to non-elected inventions.

Claims 1-4, 8-11, 13-17, 19-23, 26-28, 31 and 32 are under consideration in the instant application as they relate to DNA. Claims with limitations directed toward antisense or DNA will be considered only as they relate to DNA because all of the claims encompass DNA.

Claim Rejections - 35 USC § 101

2. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 21-23 are rejected under 35 U.S.C. 101 because they are not limited to a new and useful process, machine, manufacture, or composition of matter. Claims 21-23 are directed to use, a non-statutory claim. See MPEP 706.03(a). However, in the interest of compact prosecution, for examining purposes, the claims have been interpreted as process claims.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3, 4, 15, 16, 19-23, 26-28, 31 and 32 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 19-23, 26-28, 31 and 32 are directed toward methods of treating cancer or restinosis using retroviruses and pharmaceutical compositions thereof. At the time of filing, Feldman et al. (1995, Fundamental & Clinical Pharmacology, Vol. 9, pages 8-16) state that it is unpredictable whether therapeutic effects can be obtained against restinosis or any other disease using gene therapy because of the low efficiency of cells expressing the transgene, low transfection efficiency, the lack of target specificity, and the lack of sustained expression (page 13, column 1, second paragraph). Crystal (1995, Science, Vol. 270, page 404-410) supports the unpredictability in obtaining therapeutic effects in humans using gene therapy because of the lack of predictable expression of genes in humans (see page 409, column 1, line 22 through column 2, line 34). Thus, the major problem of gene therapy is the inability to deliver genes and obtain effective levels of expression which is dependent on the mode of delivery and the vector.

While it is relatively routine in the gene transfer art to achieve expression at non-therapeutic levels; i.e., expression at low levels or at levels providing no patentably useful phenotypic effect, it is unpredictable without specific guidance whether one will achieve expression of a gene at levels sufficient to obtain a therapeutic effect. Therefore, where there is a deficiency in the art in terms of predictability of obtaining therapeutic levels of expression, in

order to claim the benefit of therapy and to have a reasonable expectation of success in obtaining therapeutic levels of expression, the specification is required to provide embodiments or present a clear correlation between the working examples and the claimed method. The specification discloses transducing a carcinoma cell line *in vitro* with a retrovirus encoding SDI-1 and obtaining an increased proportion of the cells in G_o/G_1 (page 27, line 5). The specification does not provide adequate guidance correlating the results obtained *in vitro* to results obtained *in vivo* in such a way that one of skill would have a reasonable expectation in obtaining a therapeutic level of expression of SDI-1 such that cancer or restinosis could be treated. The specification does not teach the level of SDI-1 required to obtain a therapeutic effect, the dosage, route of administration or the desired therapeutic effect such that one of skill would be able to determine how to use the retroviral vector as a pharmaceutic composition (claims 19-20). Therefore, the specification does not enable any pharmaceutic compositions, use of a retroviral vector for treatment of disease or methods of introducing retroviral particles for the purpose of therapy as claimed.

Claims 1, 3 and 4, directed toward amino acids 1-71 or 42-58 of SDI-1, and analogues or fragments, thereof, are not enabled because one of skill would not be able to determine what applicants consider to be amino acids 1-71 or 42-58 of SDI-1. The SDI-1 gene may be identified in the art as WAF1, CIP1, PIC1 or p21 as stated in the specification on page 2, line 2. The amino acid sequence encoding SDI-1, WAF1, CIP1, PIC1 or p21 varies in the art; therefore, one of skill would not be able to determine what applicants consider amino acids 1-71 or 42-58 of SDI-1 as

claimed. Furthermore, the specification has not taught how to identify functionally useful analogues or fragments of the SDI-1 gene. It would require one of skill undue experimentation to determine what applicants consider the amino acid fragments or functional analogues claimed.

Claims 15, 16 and 20, directed toward encapsulated cells and a pharmaceutical composition comprising packaging cells, are not enabled because the only disclosed use for such cells in the specification is for administering the cells *in vivo* for the purpose of obtaining therapeutic effects and because the administration of replication competent retroviral packaging cells would most likely result in toxic, non-therapeutic results. Retroviral packaging cells are known to produce replication competent retroviral particles which, upon introduction to an individual, would prevent obtaining therapeutic effects. The specification does not provide adequate guidance such that one of skill could prevent production of replication competent retroviral particles or administer retroviral packaging cell lines such that a therapeutic effect could be obtained.

Therefore, in view of the lack of guidance in the specification regarding the level of SDI-1 required for therapy, the dosage, route of administration and the desired therapeutic effect, the lack of correlation between results obtained *in vitro* and expected results *in vivo*, the unpredictability in the art of gene therapy, the examples provided and the breadth of the claims, the ordinary artisan at the time of the instant invention would not have known how to make and/or use the claimed invention with a reasonable expectation of success.

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 9-11, 21-23 and 26 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 9-11 are indefinite because it is unclear whether the first "promoter" on line 4 of claim 9 is a target cell specific regulatory promoter or if it simply promotes expression of DNA.

Claims 21-23 provides for the use of a retroviral particle, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claims 21-23 are is rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd. v. Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Claim 26 is indefinite because it recites insertion of antisense, but depends from claim 17 which only recites genes encoding expressible SDI-1.

Claim Rejections - 35 USC § 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371© of this title before the invention thereof by the applicant for patent.

Claims 1-4 and 9 are rejected under 35 U.S.C. 102(b) as being anticipated by Tsang et al. (1994, Vaccine Res., Vol. 3, page 183-193).

Tsang et al. teach retroviral vectors comprising p21 ras and mutants of p21. Tsang et al. anticipate the claimed retroviral vectors encoding SDI-1 since p21 is involved in the cell cycle (page 185, second paragraph; page 184, line 2) and because p21 is considered to be equivalent to SDI-1 as stated in the specification on page 2, line 2. The retroviral vector taught by Tsang et al. encodes amino acids 1-71 and 42-58, as in claims 3 and 4. Thus, Tsang et al. meets all the limitations of the claims.

Claims 1-4 and 9 are rejected under 35 U.S.C. 102(e) as being anticipated by Nabel et al. (US Patent 5,863,904, Jan 26, 1999).

Nabel et al. teach adenoviral or retroviral vectors comprising p21 used to accumulate cells in G_o/G_1 (see abstract; column 3, line 10; column 4, line 60). The gene encoding p21 taught by Nabel et al. is considered equivalent to SDI-1 as claimed because both SDI-1 and p21 cause cells to accumulate in G_o/G_1 and because the specification states SDI-1 is also described as p21 as

stated in the specification on page 2, line 2 and in Nabel et al in column 1, lines 22-23. Claims 3 and 4 are anticipated by Nabel because the p21 taught by Nabel et al. encodes amino acids 1-71 and 42-58 of SDI-1 as claimed. Thus, Nabel et al. meets all the limitations of the claims.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-4, 8-11, 13-17, 19-23, 26-28, 31 and 32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nabel et al. (US Patent 5,863,904, Jan 26, 1999) in view of Haertig et al. (1993, J. Virology, Vol. 67, pages 813-821), Nakanishi et al. (1995, EMBO Journal, Vol. 14, pages 555-563) and Stange et al. (1993, Biomat. Art. Cells and Immob. Biotech., Vol. 21, pages 343-352).

Nabel et al. teach using adenoviral or retroviral vectors comprising p21 used to accumulate cells in G_o/G_1 (see abstract; column 3, line 10; column 4, line 60). The gene encoding p21 taught by Nabel et al. is considered equivalent to SDI-1 as claimed because both SDI-1 and p21 cause cells to accumulate in G_o/G_1 and because the specification states SDI-1 is also described as p21 (column 1, lines 22-23). Nabel et al. teach administering the viral vectors encoding p21 to treat restinosis (see claims) or breast cancer (column 5, line 10) as claimed

(claims 22, 23 and 28). Nabel et al. claims encapsulating the viral vector in a liposome (claim 2). Nabel et al. do not teach using the MMTV regulatory elements.

However, at the time of filing, Haertig et al. teach the MMTV regulatory elements can be used to create a chimeric retroviral vector to obtain mammary cell-specific expression of the gene of interest (see page 819, column 2, first full paragraph; page 820, column 1, last full paragraph).

Thus, it would have been obvious to combine the retroviral vector of Nabel et al. with the MMTV regulatory elements of Haertig et al. to obtain breast tissue-specific expression of SDI-1. One of skill would have recognized the ability to improve delivery of SDI-1 by directing expression of SDI-1 to breast tissue using the MMTV regulatory elements taught by Haertig et al. and would have been motivated to direct expression of SDI-1 to breast tissue to treat breast cancer since both Nabel et al. and Haertig et al. are directed to vector expression in tissues of interest. As it is unclear what is considered a therapeutic effective dose or a therapeutic effect, one of ordinary skill would have had a reasonable expectation of success in merely administering a retroviral vector as claimed and obtaining some expression. Claims 3 and 4 are obvious in view of Nabel et al. because the p21 taught by Nabel et al. encodes amino acids 1-71 and 42-58 of SDI-1 as claimed. In addition, Nakanishi et al. teach the essential elements of SDI-1 are in amino acids up to residue 71 as in claim 3 and that amino acids 49-65 can be used to make a chimeric protein which are considered equivalent to amino acids 42-58 as in claim 4 because they are the same length and in approximately the same region (see abstract). The packaging cell lines in claims 13 and 14 are obvious in view of the teachings of Nabel et al. because packaging cell lines are

required for making retroviral vectors and were well known at the time of filing. Encapsulated cells (claims 15 and 16) are obvious in view of the combined teachings of Nabel et al., Haertig et al. and Stange et al. because Stange et al. teach polyelectrolites provide an improved method of delivering cells (page 351, line 4) and because it was common practice at the time of filing to encapsulate cells to deliver cells. The limitation of injecting the retroviral vector directly to the site of the tumor (claim 31) is obvious in view of Nabel et al. who claim direct injection (see claims). Absent evidence that the particular variations of the vectors recited in claim 11 is essential to the invention, they would have represented obvious variants of any standard retroviral vector. In addition, the nomenclature of a vector is a non-effective variable routinely utilized by those of skill in the art.

Thus, Applicants' claimed invention as a whole is clearly *prima facie* obvious in the absence of evidence to the contrary.

Claims 1-4, 8-11 and 13-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Miller et al. (1989, Biotechniques, Vol. 7, pages 980-990) or Price et al. (1987, PNAS, USA, Vol. 84, pages 156-160) in view of Noda et al. (1994, Exp. Cell Res., Vol. 211, pages 90-98), Haertig et al. (1993, J. Virology, Vol. 67, pages 813-821), Nakanishi et al. (1995, EMBO Journal, Vol. 14, pages 555-563) and Stange et al. (1993, Biomat. Art. Cells and Immob. Biotech., Vol. 21, pages 343-352).

Miller et al. teach a retrovirus encoding β-gal with a 5' LTR and a human packaging cell line harboring said retrovirus (page 981, column 1, column 3). Price et al. teach the BAG

retrovirus which can be used to mark cells for detection (page 156, column 2, line 18). Miller et al. and/or Price et al. do not teach a retroviral vector encoding SDI-1 or an MMTV regulatory element.

However, at the time of filing, Noda et al. teach producing plasmids encoding SDI-1 in which expression caused the senescent phenotype (page 97, column 1, second paragraph). The plasmids of Noda et al. code for amino acids 1-71 and 42-58 as in claims 3 and 4. In addition, Nakanishi et al. teach the essential elements of SDI-1 are in amino acids up to residue 71 as in claim 3 and that amino acids 49-65 can be used to make a chimeric protein (see abstract). Amino acids 49-65 is Nakanishi et al. are considered equivalent to amino acids 42-58 as in claim 4 because they are the same length and in approximately the same region and because the amino acid sequence of SDI-1 may vary. Furthermore, Haertig et al. teach the MMTV regulatory elements can be used to create a chimeric retroviral vector to obtain mammary cell-specific expression of the gene of interest (see page 819, column 2, first full paragraph; page 820, column 1, last full paragraph).

Thus, it would have been obvious to combine the retroviral vector of Miller et al. or Price et al. with the SDI-1 gene of Noda et al. and the MMTV regulatory elements of Haertig et al. to obtain mammary cell tissue-specific expression of SDI-1. One of skill would have recognized the ability to direct expression of SDI-1 to breast tissue cell lines using the MMTV regulatory elements taught by Haertig et al. and would have been motivated to direct expression of SDI-1 to breast tissue cell lines to study breast cancer. The packaging cell lines in claims 13 and 14 are

obvious in view of the teachings of Nabel et al. because packaging cell lines are required for making retroviral vectors and were well known at the time of filing. Encapsulated cells (claims 15 and 16) are obvious in view Stange et al. by teaching polyelectrolites provide an improved method of delivering cells (page 351, line 4) and because it was common practice at the time of filing to encapsulate cells to deliver cells. Absent evidence that the particular variations of the vectors recited in claim 11 are essential to the invention, the combination of elements would have represented obvious variants of any standard retroviral vector.

Thus, Applicants' claimed invention as a whole is clearly *prima facie* obvious in the absence of evidence to the contrary.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael C. Wilson whose telephone number is (703) 305-0120. The examiner can normally be reached on Monday through Friday from 8:30 am to 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brian R. Stanton, can be reached on (703) 308-2801. The fax phone number for this Group is (703) 308-8724.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 305-0196.

Michael C. Wilson
May 24, 1999

Karen M. Hauda

KAREN HAUDA
PATENT EXAMINER